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On the Physiological Mechanisms of the Potentiation Effect of Type A and B Botulinal Toxins in the Organism[1)]

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The clarification of the mechanisms of potentiation and depotentiation of the effects of bacterial toxins in the organism is a very important problem in the pathology of infections; yet, up to now, this question still remains insufficiently explained.

According to bibliographical data, it has been established solely with relation to tetanus and botulism that their pathogenic effect increases considerably following a parenteral administration of these toxins together with heterogenic proteins (blood serum, gelatin, peptone, trypsin, etc.). Further investigations proved that the potentiation effects of the discussed toxins are neither accompanied by an increase of their quantities in the affected organism, nor by a development of new toxic products. The authors

1) - Presented December 17, 1957, at a commemoration of the scientific conference of IInd Moscow Medical Institute, dedicated to N.I. PIROGOV.

assume that the reason for similar intensification is a reduced destruction of the toxin when administered with a protein, and a preservation, by the latter, of a wide area of activity. However, none of the authors linked the potentiation phenomenon with basic points of the adaptation of toxins in the organism, nor with such disorders, which inevitably emerge as a result of the loss of functions in affected organs.

It is known that botulinal toxin excludes mainly the cholinergic sections of the nervous system, while the adrenergic neural effects are preserved. A parenteral administration of protein with species of bacterial origin leads to a notable stimulation of the adrenergic section of the nervous system and to the hyperadrenalemia.

In order to explain the degree of intensity of adrenergic processes in the dynamics of botulinal intoxication and the effects of their artificial activation, also the inhibitions upon the phenomenon of the potentiation action of botulinal toxin, we performed the following investigations: 1) determination of disorders in activities of the organs, whose functional capacity was secured by chemical agents, such as - acetylcholine and sympathin in the case of botulism of the A and B types; 2) how do the activations of pharmacological preparations of adrenoreacting and cholinereacting systems reflect themselves in the survival of animals from botulism type A and B; 3) the explanation of the role assumed by certain hormones of the hypophysial-adrenalin system (ACTH of cortisone) with relation to the phenomenon of the potentiation

action of botulinal toxin.

Investigation Methods

The experiments were performed on frogs, rabbits, cats and rats.

We investigated, on frogs, the disorders in automatic activities of the urine bladder and stomach due to botulism. We selected these organs for this reason that (according to bibliographical data) automatic contractions of the urine bladder are secured by the circulation of adrenalin in the blood and, analogous type of the stomach contractions - by acetylcholine. First, we administered to animals botulinal toxin type A (1 mouse Dlm = 0.0005 mg of dry toxin) and type B (1 mouse Dlm = 0.001 mg of dry toxin).

Frogs received their toxic injection into the spinal lymphatic sac in a quantity of 2,000 to 4,000 mouse Dlm units. On the second or third day, a heavy intoxication of frogs followed while they were kept at room temperature.

The experiments on frogs*) were carried out from the first through the seventh day after inoculation. Consequently, the animals manifested a collapse of the brain and of the spinal cord. With the dissection of the abdominal cavity, it was revealed that the apex of the urinary bladder and the pyloric section of the stomach became connected by means of serpiginous, distinct tubules. The contractions of the investigated organs were traced on a slowly rotating kymograph. The preparations were frequently humectated with

*) - Student F. GATI participated in some experiments on frogs.

RINGER'S solution in the course of experiments.

A generalised type A botulism was developed in rabbits and guinea pigs by intravenous injection of larger doses of the toxin (20,000 Dlm per 1 kg of weight) and, in cats, the type B allantiasis was developed (doses of 1,500 to 2,000 Dlm per kg of weight).

The pharmacodynamic effect of adrenalin on the heart was checked in the following way.

As a more severe dyspnea developed in poisoned rabbits and guinea pigs (after 2 to 3 hours following administration of the toxin), we performed tracheotomy and applied artificial respiration. Then,we dissected on one side of the neck the common carotid artery and we inserted cannula into it, connecting the latter with a special electrodiaphragm manometer. Having this manometer adjusted on 4-PFD-7, we recorded the contractions of the heart. We applied injections of adrenalin into the jugular vein in a quantity of 0.5 ml of 0.1% solution per 1 kg of weight, after 2 to 10 hours following the inoculation. In experiments on cats, their natural breathing was continued and the method of tracing contractions of the heart was the same as in experiments on rodents. The intoxication of cats followed after 15 to 48 hours.

We conducted the experiments on poisoned rats in two series. In the first series, we increased artificially, or decreased, the intensity of adrenergic reactions in poisoned animals by subjecting them to the action of pharmacological preparations. We used as activators of these reactions: adrenalin (0.2 ml 0.1%), caffeine (0.2 ml 20%), ephedrine (0.2 ml 2%), cocaine (0.2 ml 1%) and dysen-

teric vaccine by FLEXNER-SONNE (0.1 ml). We used tetamon-U (0.2 ml 1%) as inhibitor. We used in the second series the cholinereacting systems as activators: choline chloride (0.2 ml 2%), acetylcholine chloride (0.2 ml 0.05%) and pilocarpine (0.2 ml 0.05%). Then, we checked the clinical data pertinently to the therapeutic effect of thiamine in connection with botulism and thus we administered thiamine (0.2 ml 0.25%) to poisoned rats. In order to explain the synergism and antagonism in the action of the aforementioned preparations, we administered them in the following combinations: a) choline chloride (0.1 ml 1%) + thiamine (0.1 ml 0.25%); b) choline + thiamine (per 0.05 ml in the same concentration) + acetylcholine chloride (0.05 ml 0.05%) + tetamon-I (0.05 ml 1%).

In a series of experiments on adrenalectomized poisoned rats we investigated the effects of various doses (2.5 and 1 mg) of cortisone and ephedrine. The adrenalectomy was performed under sterile conditions in 2 to 12 days after a conducted experiment. The strength of the effects of the discussed substances was determined according to a difference between the magnitude of the experimental and the control ld_{50}. The latter was determined according to the method of REED and MUENCH. Subsequently, rats weighing 95 to 100 gm were taken to experiments in groups (16 to 24 heads in each). One group was selected for a control experiment and these animals received only pertinent doses of botulinal toxin. Four rats in remaining groups were test animals and they received, in addition to the injection of toxin, also intramuscular injection

of the investigated pharmacological preparations. Following the administration, we conducted observations for 7 days. We took into account the involved death period (days) of animals and the general percentage of lethality for each individual dose of toxin, on the basis of which we computed the magnitude of ld_{50}. The latter proved to be 0.124γ of dry toxin for healthy rats of the mentioned weight. We used the following dosages in experiments: 0.266, 0.200, 0.144, 0.098 and 0.06γ.

Inherent Investigations

We see in figure 1 that, at early stages after inoculation (1 to 2 days), while the paralytic botulinal syndrome is still absent, the automatic activities of the urine bladder and stomach do not differ from the normal ones. With average periods of development of intoxication (3d or 4th day), i.e. during the evolution of distinct paresis in the animals' muscle apparatus, automatic contractions of the urine bladder become sharply accelerated, while those of the stomach - depressed. Finally, at a late stage, with a paralysis fully developed, the automatic activities were suspended in investigated organs. We performed 25 experiments with botulinal toxin type A. The same stages of impairments in automatic activities were observed in 17 experiments on frogs poisoned with botulinal toxin type B.

No disorders in automatic contractions of the urine bladder and stomach were noted in 15 control experiments on frogs conducted in the same manner on experimental animals. Consequently, as botu-

linal intoxication of the A and B types developed in the organism of frogs, the activation of adrenoreacting systems took place and this induced, at first, a gradual acceleration in automatic activi-

Figure 1 - Disorders in automatic activities of urine bladder (I) and stomach (II) in frogs at various periods following administration of botulinal toxin. a - control on normal animals; b - automatic action prior to appearance of clinical symptoms of botulism; c - automatic action during severe paresis in skeletal muscles; d - automatic action during a full development of the paralytic botulinal syndrome. Bottom: 5-second time readings.

ties of the urine bladder and then, as the intoxication progressively developed, the exhaustion and exclusion of activities followed. At the same time, the automatic contractions of the stomach being protected by the cholinergic mechanism, became more depressed

every day after the inoculation and gradually ended.

In order to clarify, whether the accelerated activities of the adrenoreacting structures are a necessary component of the botulinal intoxication in warm-blooded animals, we performed experiments on cats and recorded the stimulation effects of the cervicosympathetic nerve on the respiratory center and on the blinking of the ocular membrane. The effect of the sympathetic nerve on the respiratory center, just like the automatic activity of the urine bladder in frogs, is protected by the mediatory mechanism - sympathin, whereas the effect of the sympathetic nerve on the third eyelid does not undergo any noticeable changes under the impairment conditions in the formation of sympathin, following a removal of the chromaffin tissue in the adrenal glands.

Since the experiments were conducted with the type B botulinal toxin, thus at the beginning of the work we made a comparison of the mechanism of the pathogenic effect of the type B toxin with that of the type A. The results of the investigation of the type A toxin were published earlier. In 22 experiments with the type B toxin we made the following observations: according to analogy with the type A toxin, the exclusion of the inhibitory effect of the vagus nerve on the heart took place with a development of the paralytic botulinal syndrome. A preliminary section of one of the cervicosympathetic nerves, in the course of the following 7 experiments, i.e prior to administration of the toxin, fully protected the peripheral area of the cut-off nerve from the paralytic effect of the toxin,

just like in the case of administered type A botulinal toxin. Thus, not only the clinical picture, but also the mechanism of the affection by botulinal toxin type B showed its complete identity with the action of the type A toxin.

The effect of the cervical truncus sympathicus on respiration and on the blinking membrane of the eye was studied in 32 experiments on poisoned animals, and in 14 experiments on healthy ones. At the same time, we discovered in 16 experiments that a stimulation[1] of the preganglionic fibers in the cervicosympathetic nerve in animals, during a development of the paralytic botulinal syndrome of a mild and average severity (i.e up to the stage of developed paresis in skeletal muscles), resulted in a distinct activation of the sympathetic effect on the respiratory center; the intensification by 2 to 5 times, and the increase of frequency in respiratory movements, occurred even in the presence of the stimulating current of 0.6 to 1 v (norm: 4 to 10 v; figure 2).

In similar experiments substantial changes also appeared in the type of contractions of the third eyelid, namely a pessimum of the frequency during a prolonged stimulation of the nerve occurred only with frequencies of 260 to 310 cps (norm: 164 to 190 cps), but after stimulation of the postganglionic fiber in the same nerve, no observable deviation from the norm was detected in the pessimum of the frequency stimulation; the inhibition of the pessimum followed in all experiments with the frequencies of 120 to 200 cps. Conse-

1) - Stimulator GRAEH-1. Frequency 1 to 780 cps; the duration of the single square pulse 3.5 m/sec.

quently, the cause of the frequency stimulation displacement was, obviously, a change in the functional characteristics of the ganglion itself.

Another pattern was observed with the development of a severe paralytic syndrome. As a rule, the sympathetic effect on the respiratory center weakened sharply in 16 experiments and, frequently, collapsed (see figure 2). The effects were absent even during stimulation of the sympathetic nerve by the current of 10 to 40 v. Meanwhile, the contractions of the blinking membrane in the eye occurred in most experiments in response to the same stimulating current, as in previous experiments (1 v), and only in two experiments in response to 10 v. The inhibition of the pessimum appeared approximately in response to the same frequencies (220 to 300 cps). The submitted data show that, during a more severe intoxication with botulism, the transmittal of the stimulation was preserved by way of the upper cervicosympathetic ganglion. Figure 2 shows that the stimulation of the cervical sympathicus leads to a contraction of the third eyelid, however the mediatory effect on the respiratory center is discontinued.

Thus, in warm-blooded and cold-blooded animals the mediatory component of the sympathetic effect on tissues becomes considerably activated during the initial stages of botulinal intoxication, but, as a development of the disease progresses, it weakens sharply and frequently disappears. Here the question arises: is the discontinuance of the sympathetic effects not a resultant fact of the adrenoreacting structures' exhaustion due to extremely stimulating

influences of sympathin (adrenalin)?

In connection with this, investigations of the pharmacodynamic

Figure 2 - Disorders in the sympathetic effect on respiration and on the blinking membrane of the eye in cats at various periods following the administration of botulinal toxin type B. a - effect on respiration following the stimulation of the cervicosympathetic nerve in normal animals (control); b - the same in the presence of observable paresis in skeletal muscles (average range of inoculation); c - the same with the development of a severe paralytic syndrome; d - effect on the third eyelid following a stimulation of the cervicosympathetic truncus on the background of a severe generalized botulism (the frequency of stimulating current is marked on the curve). Time mark: 5 seconds.

effects of adrenalin were conducted with tissues of animals in various

stages of botulinal intoxication. The object of studies was the heart, which, as we know, possesses a high sensitivity to humoral agents. We performed experiments on cats with botulinal toxin type B and, on rabbits and guinea pigs, with the type A toxin.

In 15 experiments on cats, conducted during the light and average stages of the development of botulinal paralytic syndrome (18 to 28 hours after inoculation), the heart reaction to intravenous administration of 0.1% adrenalin, in 0.5 ml dose, showed a marked inversion. Also the bradycardia reflex was completely discontinued in all 16 control experiments conducted on normal animals and the acceleration of rhythmic cardiac contractions followed. The

Figure 3 - Toxic effect of adrenalin on heart of a rabbit exposed to botulinal toxin. Time mark: 1/4 of a second. Arrow indicates an instant of administration (into external jugular vein) of 1 ml of adrenalin solution in a concentration of 1×10^{-3} gm/ml.

expressed positive inotropic effect, according to magnitude, proved to be close to normal (in 1½ - 4 times). Apparently, the absence of bradycardia resulted from injuries to the vagus nerves' centers at this stage of inoculation.

In 10 experiments involving a severe stage of botulism (almost a complete paralysis), the administration of analogous dose of adrenalin (unlike in previous experiments) resulted only in a slight

intensification of heart contractions (by 14 to 70%) and, in some instances, the positive inotropic effect was completely absent. However, in these experiments, the positive chronotropic effect of adrenalin was usually preserved.

Identical data were obtained following the inoculation of 16 rabbits and 10 guinea pigs with the type A botulinal toxin. It should be noted that, in the presence of a severe stage of intoxication in rabbits, one could observe frequently a toxic effect from adrenalin injections.

The results of the experiments proved that the administration of adrenalin within the first 3 to 3½ hours after inoculation showed the same positive inotropic and chronotropic effects as in similar experiments on poisoned cats. However, the administration of the same quantity of adrenalin later than the indicated time (by 4 to 10 hours after inoculation) caused, in most experiments, a development of acute cardiac insufficiency. Figure 3 shows that the injection of adrenalin into the blood caused a brief positive inotropic effect, but, 2 minutes later, an acute cardiac insufficiency followed and death of the animal resulted.

In 12 control experiments we administered, instead of adrenalin, the injection of acetylcholine chloride (1 ml 0.01%), methionine (2 ml 20%), thiamine (2 ml 5%), ascorbic acid (2 ml 1%), blood serum of guinea pig (2 ml) and antibotulinal serum type A (25,000 to 40,000 BU); at the same time, we did not detect even a single case of a similar cardiac insufficiency.

Thus, on the basis of the conducted experiments, we can conclude

that, in the case of botulism, the action of adrenalin, as well as the sympathetic effect, undergo two phases of changes: a slight activation in the initial stages and a considerable weakening during a severe intoxication. Apparently, the cause of a similar disorder is a decline in the capacity of adrenoreacting structures to react on specific stimulus, i.e. sympathin (adrenalin). We assume that the functional condition of adrenergic mechanisms plays an essential role in the course and severity of botulinal intoxications.

Proceeding from this hypothesis, we attempted to clarify a point, how does the intensity of adrenergic processes reflect itself in the survival of animals poisoned with a lethal dose of botulinal toxin. Consequently, we made experiments on rats. We administered adrenalin to one group of rats and, to the other group, the preparations which stimulated the sympathetic section of the nervous system: ephedrine, caffeine, cocaine and dysenteric vaccine by PLESSAR-SONNE. Cocaine, in addition to stimulating the nervous system, also caused a sensitization of tissues to adrenalin. As an index of the effectiveness of the examined substances, we used the difference between the sizes of the experimental and control ld_{50}.

Regardless of a quick inactivation of adrenalin in the organism, daily injections of adrenalin possessed a considerable potential effect.

The ld_{50} is 0.034 g or dry toxin proved to be below the control standard (ld_{50} for a group of animals which received no indicated preparations). A distinct potential effect was observed after administration of ephedrine, caffeine, cocaine and dysenteric vaccines.

With the administration of ephedrine, the ld_{50} was less than 0.060γ, i.e. more than 0.064γ below the control; with the administration of caffeine, it was by 0.050γ below the control; cocaine: by 0.016γ, and dysenteric vaccines: by 0.034γ. Consequently, a relatively long stimulation, produced in adrenoreacting systems with a single administration of the indicated substances, developed a considerable aggravation in the course of botulinal intoxication.

The next series of experiments were intended to clarify whether the gravity of the disease declines with the inhibition of adrenergic processes. A similar inhibition was caused by a ganglioblocking preparation of tetamon-I (tetraethyl ammonium iodide), which blocks the transmittal of impulses in sympathetic and parasympathetic ganglions without stimulating the latter first. The experiments showed that blocking of the sympathetic section of the nervous system leads to depotentiation effects of botulinal toxin. Following the administration of tetamon-I, the ld_{50} moved higher than that of control by 0.064γ. Thus, the results of these experiments proved again that the stimulation of adrenergic systems in the organism leads to a potentiation of the effects of botulinal toxin.

Finally, we conducted experiments designed to clarify the role of the cholinoreacting systems in dynamics of botulinal intoxication. We activated these systems in poisoned animals by a parenteral administration of choline chloride, acetylcholine chloride and pilocarpine. The obtained results indicated that choline chloride and acetylcholine administered to animals poisoned with botulinal toxin

possessed a distinct therapeutic effect: the magnitude of the ld_{50} after injections of acetylcholine was 0.052γ and after administration of choline, it went even higher to 0.076γ above the control. However, the administration of pilocarpine resulted in a distinct potentiation effect of the toxin: the ld_{50} was reduced to 0.030γ below the control. Consequently, only acetylcholine chloride and choline chloride possess depotentiation properties.

Apparently, the effects of these substances can be explained by this: as they participate in the trophic system of the cholinergic section of the nervous system, they prevent the pathogenic effect of the toxin to a certain extent. This conclusion was verified in experiments with pilocarpine. The latter also stimulates the cholinereacting systems, but unlike choline and acetylcholine, it is not a nutrient substance for neural tissues. In connection with this, the stimulation of the cholinereactive systems, as well as adrenoreactive, leads to a distinct potentiation of botulinal toxin. A specific trophic importance of choline substances was revealed in four control experiments conducted on rats treated with acetylcholine chloride. In spite of the administered toxin to these animals, they did not manifest any disorders in the inhibiting effect of the vagus nerve on the heart.

On the basis of obtained data we can assume that a disorder in the acetylcholine metabolism in the nervous system plays an important role in the pathogenesis of botulism and, at the same time, the neural tissues obviously protect the opportunity to utilize (for their vital activities) the parenterally administered pharmacological

acetylcholine. In connection with this, we tried to clarify, whether it is possible to increase the resistance of organism to botulinal toxin by administration of preparations, which intensify the synthesis of acetylcholine. As we know, thiamine participates in the synthesis of acetylcholine and, according to one clinical report, it shows a therapeutic effect traceable to botulism in man. We conducted experiments with thiamine aiministered to poisoned animals; at the same time we discovered that, after administration of thiamine, the magnitude of the ld_{50} was higher by 0.016γ than that of control.

Thus, it is probable that thiamine is able to activate the formative processes of acetylcholine during botulinal intoxication, however its action is less distinct than that of choline and acetylcholine. Next, we tried to restore the cholinergic processes disturbed due to poisoning and we administered a combination of thiamine with choline. The results of the experiments proved that, in this case, the ld_{50} exceeded the control by 0.094γ, i.e. the mixture possessed a considerable depotentiation effect, while a combination of choline + thiamine + acetylcholine + tetamon-I indicated a lower depotentiation effect: ld_{50} exceeded the control only by 0.001γ. We are inclined to explain a similar result by decreased quantities of choline and acetylcholine in the mixture.

It should be pointed out that, in order to manifest their therapeutic effects, choline chloride and acetylcholine chloride are required to remain in the organism for a considerable time. All our attempts, made according to rules of experiment, to restore the lost

inhibitory effect on the heart in rabbits poisoned with botulinal toxin were unsuccessful, and administration of choline and acetylcholine into the blood stream proved fruitless.

Consequently, three rules revealed themselves in the course of our investigation as to the role of the adrenoreacting and cholinereacting systems during experimental intoxication with botulism: 1) the stimulation of adrenoreacting systems leads to a noticeable potentiation effect of botulinal toxin in the organism; 2) a similar effect possess preparations, which stimulate cholinereacting systems, but they are not used by neural tissues as nutritive substances; 3) choline chloride and acetylcholine chloride, in spite of their stimulative effects on cholinereacting systems, show a distinct depotentiation effect in the presence of experimental botulism. This indicates that an injury in the cholinergic section of the nervous system apparently occurs as a result of its depressed trophism induced by a disturbance in the acetylcholine metabolism, which is caused in the organism by the toxin.

Currently, a wide acceptance received a theory about the role of the hypophysial-adrenalin system in realization of protective reactions in the organism against various harmful effects (SELYE, 1950). In connection with this, we regarded as expedient to explain the participation which certain hormones of a designated group of endocrine glands assume in the phenomenon of the potentiation effect of botulinal toxin. It is known that the resistance of rats to diphtheria toxin is considerably reduced by way of adrenalectomy due to the

loss of many steroid hormones in the organism.

The experiments with botulinal toxin were performed on 7 groups of rats (16 to 20 heads in each) according to the same method, as in previous series. At the same time, we used three groups of intact animals to investigate the effects of ACTH (6 units per day) and cortisone (in daily doses of 2.5 and 1 mg). We used the next four groups (which included adrenalectomized animals) on the 2nd and 12th day after the operation, in order to study the effects of adrenalectomy on the course of botulinal intoxication and, at the same time, the effects of various doses (2.5 and 1 mg) of cortisone and the effects of the vigorously potentiating agent like ephedrine (in the same doses), all on intact animals in analogous experiments. The adrenalectomy reduced the resistance of rats to botulinal toxin, however the effect of adrenalectomy was considerably milder in comparison with the effects of sympathomimetic preparations. The adrenalectomy did not eliminate the potentiating effect of ephedrine and that of a larger dose of cortisone (2.5 mg). The administration of cortisone in a dose of 2.5 mg to intact animals also induced potentiation; a slightly depotentiating effect was observed only with 1 mg dose. The latter effect was preserved in adrenalectomized animals. The ACTH injections brought negative results.

On the basis of the experimental data we can come to a conclusion that, although hormones of the hypophysial-adrenalin system are (to a familiar extent) involved in the phenomenon of potentiation of the pathogenic effect of botulinal toxin, yet, obviously, the basic role in this process play adrenergic reactions.

Conclusions

1. It is obvious that the mechanism of the pathogenic effect of botulinal toxins type A and B are identical.

2. A profound disorder in the synergy between the adrenergic and cholinergic processes emerges in the course of botulinal intoxication together with the paralysis of cholinergic nerves. Consequently, during initial stages of intoxication, the activation of the adrenergic effect on tissues occurs, and its weakening, or even a frequent exclusion, follows during severe stages. The reason for a similar effect is a decrease in the sensitivity of tissues in the affected organism to the mediatory component of the sympathetic effect.

3. The artificial stimulation of adrenergic processes by pharmacological or bacterial means results in a noticeable potentiation of the pathogenic effect of botulinal toxin, whereas the inhibition of these processes leads to a depotentiation of a similar effect.

4. The preparations which stimulate the M-cholinereacting systems possess the potentiation effect; however, choline chloride, acetylcholine chloride, thiamine and their combinations manifest a distinct depotentiation effect with relation to botulinal toxins.

5. The potentiation phenomenon in the pathogenic effect of botulinal toxin by way of stimulation of adrenergic processes does not undergo any substantial changes in adrenalectomized rats.

6. The administration of cortisone-acetate in a dose of 1 mg

per 0.1 kg of animal's weight produced insignificant effect on the survival of rats affected by botulism, whereas the administration of a dose of 2.5 mg per 0.1 kg of weight resulted in the potentiation of the effect of toxin.

7. The administration of ACTH in a dose of 6 units per 0.1 kg of animals' weight failed to produce ary changes in the effect of botulinal toxin in a dose administered by us.

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Summary (copied)

An attempt was made to reveal the role of mediator component in potentiation of the botulism action. The author demonstrated that artificial stimulation of adrenergic processes in the poisoned body by pharmacological or bacterial means results in considerable potentiation of the pathogenic effect of this toxin. On the contrary, depression of these processes by a ganglioblocking preparation (tetamon-I), or activation of cholinreactive systems by cholinchloride and acetylcholinechloride decreases the pathogenic effect of botulism.